

**What is claimed is :**

1. A method for the screening of a non-recombinant cell line capable under appropriate conditions, of exhibiting an upregulated expression of a target protein, preferably of an isoenzyme of PDE4, naturally expressed in said cell, said method comprising:

- providing a non-recombinant cell line;
- treating said non-recombinant cell line with a concentration of a phorbol ester, preferably PMA, ranging from 0.1 to 3  $\mu$ M for a period of time ranging from 12 hours to 10 days, and
- measuring the amount of target protein produced by said treated non-recombinant cell line and comparing the measured amount with the amount of protein produced under normal culturing conditions by the non-recombinant cell line prior to PMA treatment.

2. A method for the screening of a candidate molecule that modulates the expression or the activity of the human phosphodiesterase 4A (PDE 4A), said method comprising the steps of :

- a) incubating non-recombinant cells, preferably cells from a HL60 cell line, in the presence of a concentration of a phorbol ester, preferably phorbol myristate acetate (PMA), which is sufficient to significantly upregulate PDE4 expression in said cells;
- b) adding a candidate molecule to the culture medium in which the phorbol ester-treated cells are cultured;
- c) harvesting and disrupting the cells; and
- d) quantifying the cAMP content in the cell lysate.

3. The method of claim 2, wherein the cAMP content measured in step d) is compared with the cAMP content in the cell lysate of the phorbol ester treated cells cultured in the absence of the candidate molecule.

4. The method of claim 2, wherein the phorbol ester is present in the culture medium at a concentration ranging from 0.5 to 1.5  $\mu\text{M}$ .

5 5. The method of claim 2, wherein the phorbol ester is present in the culture medium at the concentration of 1  $\mu\text{M}$ .

6. The method of claim 2, wherein the quantification of cAMP content is performed on the cytosolic fraction of the cell lysed.

10 7. A method for determining the selectivity of a candidate molecule for a PDE4 subtype, said method comprising:

- 15 - providing a non-recombinant cell line culture presenting a significantly upregulated expression of a PDE4 isoenzyme and a substantially downregulated expression of other PDE4 isoenzymes, preferably unmeasurable levels of all other PDE4 isoenzymes ;
- adding said candidate compound to said cell line culture; and
- quantifying the variation of cAMP contents in said culture.